

## Study Protocol And Rationale Phentermine-Topiramate ER

### Study Protocol And Rationale For A Randomized Double-Blinded Crossover Trial Of Phentermine-Topiramate ER Versus Placebo To Treat Binge Eating Disorder And Bulimia Nervosa

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## **Abstract**

**Introduction:** Bulimia nervosa (BN) and binge eating disorder (BED) are associated with severe psychological and medical consequences. Current therapies are limited, leaving up to 50% of patients symptomatic despite treatment, underscoring the need for additional treatment options. Qsymia, an FDA-approved medication for obesity, combines phentermine and topiramate ER. Topiramate has demonstrated efficacy for both BED and BN, but limited tolerability. Phentermine is FDA-approved for weight loss. A rationale for combined phentermine/topiramate for BED and BN is improved tolerability and efficacy. While a prior case series exploring Qsymia for BED showed promise, randomized studies are needed to evaluate Qsymia's safety and efficacy when re-purposed in eating disorders. We present a study protocol for a Phase I/IIa single-center, prospective, double-blinded, randomized, crossover trial examining safety and preliminary efficacy of Qsymia for BED and BN.

**Methods:** Adults with BED (n=15) or BN (n=15) are randomized 1:1 to receive 12 weeks Qsymia (phentermine/topiramate ER, 3.75mg/23mg-15mg/92mg) or placebo, followed by 2-weeks washout and 12-weeks crossover, where those on Qsymia receive placebo and vice versa. Subsequently participants receive 8 weeks follow-up off study medications. The primary outcome is the number of binge days/week measured by EDE. Secondary outcomes include average number of binge episodes, percentage abstinence from binge eating, and changes in weight/vitals, eating psychopathology, and mood.

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**Discussion:** To our knowledge this is the first randomized, double-blind protocol investigating the safety and efficacy of phentermine/topiramate in BED and BN. We highlight the background and rationale for this study, including the advantages of a crossover design.

**Keywords:** Binge Eating Disorder, Bulimia Nervosa, Obesity, Clinical Trial, Qsymia, Phentermine, Topiramate, Eating Disorder Treatment

**Abbreviations:** 5' Adenosine monophosphate-activated protein kinase (AMPK), Binge Eating Disorder (BED), Binge Eating Scale (BES), Bulimia Nervosa (BN), Cognitive Behavioral Therapy (CBT), Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), Dialectical Behavioral Therapy (DBT), Eating Disorder Examination (EDE), Eating Disorder Examination Questionnaire (EDE-Q), Gamma-aminobutyrate (GABA), Interpersonal Psychotherapy, Lisdexamfetamine (LDX), Patient Health Questionnaire (PHQ-9), Randomized Clinical Trials (RCTs), Selective Serotonin Reuptake Inhibitors (SSRIs), Three Factor Eating Questionnaire (TFEQ), Yale Food Addiction Scale (YFAS), Yale-Brown Obsessive Compulsive Scale for Binge Eating (YBOCS-BE)

## **Introduction**

Binge eating disorder (BED) and bulimia nervosa (BN) are serious disorders associated with adverse psychological and medical consequences. Both are characterized by repeated binge eating (i.e., consuming unusually large amounts of food over a discrete period of time with a sense of loss of control), with BN also involving compensatory behaviors to prevent weight gain (e.g., self-induced vomiting; misuse of laxatives, diuretics, or enemas; excessive exercise; and/or fasting).

Patients with BED or BN frequently suffer from co-occurring psychiatric disorders (e.g., mood, anxiety, substance use disorders) compared to the general population.<sup>1, 2</sup> Approximately 40 - 80% of those with BN or BED are obese.<sup>3</sup> Physical co-morbidities associated with both binge eating and obesity include diabetes, hypertension, dyslipidemia, coronary heart disease, congestive heart failure, gout, and various types of cancer. BED and BN are associated with increased healthcare costs in addition to reduced quality of life and increased morbidity and mortality.<sup>4, 5</sup>

The lifetime prevalence in the US adult population of BED is estimated to be 3.5% among women and 2% among men.<sup>6</sup> The prevalence of BED is increasing, with true prevalence likely underestimated due to the tendency of patients to conceal their illness. The prevalence of BN is lower, estimated on average to fall within 0.5 – 1.5%,<sup>2</sup> with women comprising the majority, roughly 90% of those diagnosed.<sup>7</sup>

## **BED – Current Treatment**

Current treatment options for BED include psychotherapy and pharmacotherapy. Randomized studies have demonstrated the effectiveness of therapist-led Cognitive Behavior Therapy (CBT) in reducing binge frequency and promoting abstinence, with benefits persisting for at least 1 year after treatment completion.<sup>8,9</sup> Non-therapist led CBT (e.g., CBT guided self-help) has also demonstrated efficacy, though overall there is less evidence for benefit.<sup>10</sup> Other behavioral treatment modalities include interpersonal psychotherapy (IPT),<sup>11</sup> dialectical behavioral therapy (DBT),<sup>12</sup> behavioral weight loss, and mindfulness training.<sup>10,13</sup> When averaging across multiple trials, abstinence after psychotherapy, including CBT, is about 50%, leaving up to half of patients still symptomatic after treatment.<sup>14</sup>

Randomized controlled trials involving pharmacotherapy demonstrate some improvement in binge eating behaviors with antidepressants such as fluoxetine at 60-80mg,<sup>8,15</sup> fluvoxamine 50-300mg,<sup>16</sup> sertraline 50-200mg,<sup>17</sup> citalopram 40-60mg,<sup>18</sup> duloxetine 30-120mg,<sup>19</sup> and high-dose escitalopram 10-30mg,<sup>20</sup> but have not shown a significant influence on long-term weight loss. In the studies, treatment periods ranged between 6-12 weeks, and while there was some improvement in short-term weight reduction with some SSRIs, many are associated with weight gain when used long-term.<sup>21</sup> Other controlled studies or case series have shown some success with baclofen,<sup>22</sup> atomoxetine,<sup>23</sup> venlafaxine,<sup>24</sup> and a combination of bupropion/naltrexone.<sup>25</sup> Randomized studies with the anticonvulsant topiramate have shown improvement in both binge eating and weight at doses ranging from 150mg up to 600mg.<sup>26,27</sup> A recent systematic review and meta-analysis found that both lisdexamfetamine (LDX) and topiramate each reduced binge eating frequency and decreased weight in adults with BED.<sup>10</sup> Currently, only LDX at 50-70mg

daily is FDA-approved for the treatment of moderate-severe BED, based on 12-week phase III data demonstrating a significant binge reduction of  $4.1 \pm 1.6$  binge days on the 70mg dose compared to  $3.3 \pm 2.0$  binge days on placebo.<sup>28</sup> Abstinence rates from bingeing over a 4-week period were significantly greater than placebo with 50% on LDX 70mg compared to 21.3% on placebo.<sup>28</sup> Importantly, the use of LDX is restricted due to its classification as an FDA schedule II controlled substance.

### **BN – Current Treatment**

Current treatment strategies for BN have incorporated psychotherapy (e.g., CBT), and/or pharmacological agents. Empirical evidence with regard to psychotherapy for BN supports the use of CBT as first-line treatment in reducing binge eating and purging.<sup>29,30</sup> Abstinence rates across multiple trials are about 30-50% after CBT, which leaves about 50-70% still symptomatic after treatment.<sup>14</sup>

Several randomized controlled trials of pharmacologic agents have demonstrated significant reductions in bulimic behavior. While the pharmacological targets in BN are similar to BED, not all SSRIs are equally effective. The most studied medications are fluvoxamine (not shown to be superior to placebo) and fluoxetine (estimated relapse rate of 19% at 3 months and 33% at 12 months), which received an FDA indication after demonstrating superiority to placebo at a high dose of 60mg/day in reducing binge and purge frequency.<sup>31,32</sup> Marrazzi et al. and colleagues (1995) conducted a double-blind placebo-controlled crossover study showing benefit of naltrexone in reducing binge and purge episodes.<sup>33</sup> One randomized trial demonstrated benefit of the antiemetic ondansetron, a 5HT<sub>3</sub>-antagonist, in reducing both bingeing and purging, although this medication is generally used in refractory cases due to cost.<sup>34</sup> Topiramate,

described in detail in the next section, has shown effectiveness for both BN and BED as well as obesity, but its widespread use is limited due to decreased tolerability in higher doses.<sup>35</sup>

### **Treatment Gap**

Current pharmacologic and psychotherapeutic treatments for BED and BN, while helpful, still leave up a significant portion, up to 50% for BED and up to 70% for BN, of patients symptomatic at the end of therapy. The limited benefit of current treatments underscores the importance of exploring new treatment options. As 40-80% of patients with BED or BN are obese, weight loss is an important target to reduce medical sequelae. While on average there is short-term weight reduction for BED and BN using SSRIs, long-term use is associated with weight gain.

### **Qsymia And Rationale For Use**

The FDA has approved several medications or medication combinations for the treatment of obesity, but these have not been tested formally in RCTs for use in BED or BN. Examples include combined phentermine/topiramate ER, combined naltrexone/bupropion, lorcaserin, and liraglutide. The combination drug Qsymia, FDA-approved for obesity in 2013, is composed of phentermine and extended-release topiramate.

Phentermine, originally approved in 1959, is a sympathomimetic amine and anorectic agent FDA approved for short term treatment of obesity. While it is a structural analogue to amphetamine, it is categorized as a class C Schedule IV controlled medication; clinical intervention trials have shown a lack of withdrawal symptoms upon abrupt cessation, even in patients who have been

taking the medication for decades. In particular, Hendricks and colleagues reported that phentermine did not induce physiological dependence or craving.<sup>36</sup> At low doses contained in Qsymia, phentermine works centrally through the release of norepinephrine in the hypothalamus, resulting in reduced appetite and decreased food consumption. There is weak activity on the dopamine transporter and even weaker activity on the serotonin transporter.<sup>37</sup> Common side effects of phentermine include dry mouth and insomnia, which typically improve over time with continued use. Phentermine has not been studied independently as an agent for treatment of BED or BN. In one small open label trial, patients were offered phentermine in combination with both fluoxetine and psychotherapy (CBT). Significant reductions in binge frequency as well as weight loss were found at post-treatment but weight regain and increases in binge eating were found with cessation of medications.<sup>38</sup> Five of 12 patients discontinued phentermine primarily due to perceived lack of efficacy after being on the drug over time. Without a control group, separation of the effects of medication from psychotherapy is not possible.

Topiramate was FDA-approved for the treatment of epilepsy in 1996 and for migraine prophylaxis in 2004. It has multiple mechanisms of action which are not fully understood. Its pharmacologic effects include blockade of voltage-gated sodium channels, enhancement of gamma-aminobutyrate activity (GABA), antagonism of glutamate receptors, and inhibition of carbonic anhydrase. It has been suggested that topiramate may have effects on insulin signaling and hypothalamic leptin as well as AMP-activated protein kinase (AMPK) signaling in peripheral tissues.<sup>39</sup> Topiramate's exact mechanism of anorexic action is largely unknown, but its effects may be due to both appetite suppression and satiety enhancement. Topiramate has been shown to be effective in reducing binge eating in patients with both BED and BN.<sup>10</sup>

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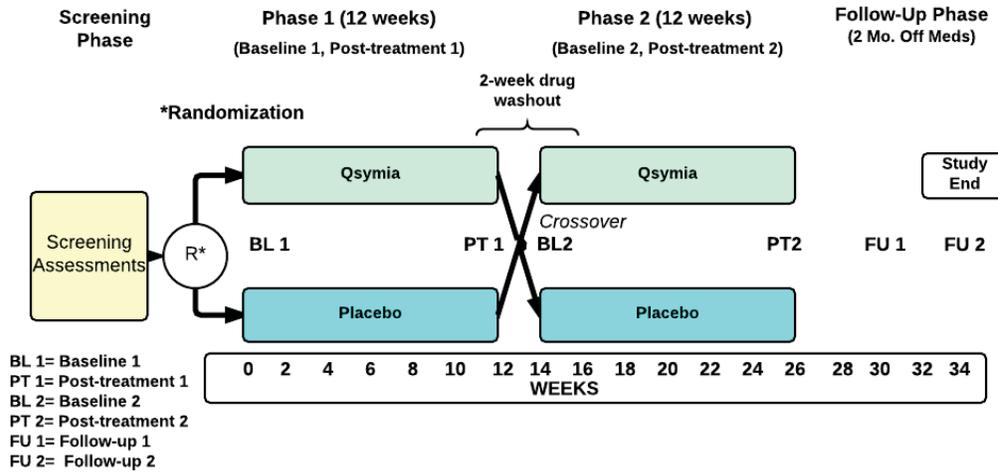
However, the drop-out rates due to side effects in topiramate studies have been high (up to 50%). These side effects primarily include sedation, memory/concentration impairment and parasthesias.<sup>35</sup>

A key rationale for investigating Qsymia in patients with BED or BN is to reduce the likelihood of adverse side effects by using a combination of drugs with opposing side-effect profiles. The stimulant-like properties of phentermine can act to reduce the cognitive and sedative side effects of the topiramate, potentially lowering discontinuation rates.<sup>37</sup> In addition, Qsymia may have synergistic effects, allowing for lower doses and enhanced efficacy of both drugs compared to monotherapy. For example, phentermine/topiramate ER resulted in a 29% lower maximum plasma concentration of topiramate compared to topiramate monotherapy. The combination formulation allows for peak exposure of phentermine in the morning and peak exposure of topiramate ER to occur in the late afternoon and evening compared to monotherapy.<sup>40</sup> The differences in the pharmacokinetic profile of the combination of phentermine/topiramate ER may be responsible for the improved efficacy (in terms of greater weight loss) that was found in obesity studies.<sup>41</sup> Of note, a recent case series showed Qsymia resulted in reductions in binge eating behaviors and clinically significant weight loss in patients with BED and co-morbid obesity.<sup>42</sup> The drug was very well-tolerated and no side effects were reported. To date, Qsymia has not been tested in double-blinded randomized studies for BED or BN, which provided the impetus for the design of the present protocol.

**Methods  
Procedure**

The study was reviewed and approved by the Institutional Review Board of Stanford University Medical Center. The research is being conducted in the Department of Psychiatry and Behavioral Sciences and is carefully monitored (protocol # 31390) by a Data Safety Monitoring Board at Stanford University. This is a randomized double-blinded placebo-controlled crossover trial totaling 34 weeks in length with ongoing enrollment of adults with BED (up to n = 15) and BN (up to n= 15). Patients are randomized to identical appearing placebo or Qsymia with 4 standard FDA-approved doses of phentermine/topiramate ER: 3.75mg/23mg; 7.5mg/46mg; 11.25mg/69 mg; and 15mg/92mg. The oral administration follows a weekly titration increase as follows: The four doses of Qsymia are titrated in a gradual fashion weekly over the course of four weeks, beginning with the lowest standard dose of phentermine/topiramate (3.75 mg/23 mg) up to the highest standard dose (15mg/92 mg) as tolerated. Each week of the 4-week ramp up period, the dose is increased to the next standard dose, provided no major side effects are reported. The final dose prescribed will be the minimum dose at which effects are seen and side effects are tolerable. Patients are randomized to 12 weeks of treatment with Qsymia or placebo, then a 2-week washout followed by a crossover of 12 weeks (total 26 weeks) and a final 8 weeks of follow-up while off medications, totaling 34 weeks (Figure 1). The washout period of two weeks was chosen to account for sufficient time to allow completion of at least five half lives, given a half-life in plasma of twenty hours for phentermine and sixty-five hours for topiramate. Per the protocol, subjects will be expected to attend 12 study visits spaced 2-4 weeks apart. Compensation in the form of giftcards of twenty US dollars will be given for completion of each assessment: post-treatment 1, post-treatment 2, follow-up 1 and 2 assessments. For participants who complete all four assessments, an additional twenty US dollars will be given.

**Figure 1.** Study Design



### Sample Size and Statistical Power

This RCT crossover study is designed to test for a clinically meaningful difference in number of binge days (primary study outcome) when comparing drug to placebo. Assuming a standard paired t-test we estimated that for 80% power, a significance level of 0.05, and a standardized treatment effect size of 0.6 a total of 24 subjects are required. The standardized treatment effect of 0.6 was estimated based on previous studies of topiramate.<sup>43, 27</sup> To account for an estimated drop out rate of 20%, the minimum sample size requirement was inflated accordingly to 30 subjects. The paired t-test requires differences to be normally distributed. Should the differences be substantially non-normal, the t-test would no longer be the optimal test with respect to power and the estimated sample size would be slightly conservative.”

### Randomization Procedure

Eligible participants are randomly assigned to medication group 1 or 2; a cross-over protocol follows the first phase of the trial. This is to be done by randomization as they are sequentially

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determined to be eligible for the study. Eating disorder diagnoses (BN and BED) are being recruited and randomized separately to ensure even distribution of diagnoses in each medication group. Five blocks of six permutation identifications were created and a treatment group assigned to each ID. Each treatment group will be shuffled within each block using the RAND function in Excel (Microsoft). This schedule and randomization was determined by the study research coordinator and reviewed by a statistician prior to study initiation.

### **Participants: Inclusion/Exclusion Criteria**

Adults age 18 to 60 are being recruited via online advertisements, newspaper, flyers, and referrals from local clinics within the community since July 2015. Inclusion criteria are: (a) meet DSM-5 criteria for BN or BED refractory to prior treatment, (b) have a BMI of 21 or greater, (c) if female with child-bearing potential, must have an initial negative pregnancy test and have adequate birth control measures, (d) must be medically stable with no new diagnoses (medical, surgical, or psychiatric) within the past 6 months, (e) must be able to comply with all 12 study visits, treatment plans, and blood draws at Stanford. Exclusion criteria include: (a) any patient with bipolar disorder or schizophrenia, any patient taking a mood stabilizer or antipsychotic medication within the past 3 months of enrollment, or any patient on an unstable SSRI dose (change in dosage over the prior 30 days), (b) any patient with current or past history of anorexia nervosa (including BMI < 17.5), (c) any history of prior (within 30 days) use of over the counter weight-reducing agents or herbal preparations, (d) any prescription weight loss medication within 3 months of enrollment, (e) any patient who started a psychological weight-loss intervention (e.g. Weight Watchers, Jenny Craig) within the prior month or if started over a month and achieved weight loss, (If no weight loss was achieved in over a month, eligibility was considered provided willingness to discontinue the weight intervention) (f) currently receiving

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therapy with a psychostimulant or used a psychostimulant within past 6 months of enrollment, (g) any known sensitivity to phentermine or topiramate, (h) change in thyroid, psychiatric (e.g., antidepressant), or blood pressure medications within the past one month, (i) on a potassium-wasting diuretic, (j) on a carbonic anhydrase inhibitor such as zonisamide or acetazolamide, (k) on insulin or an insulin secretagogue, (l) liver enzymes at baseline greater than three times the upper limit of normal, (m) any baseline potassium of less than 3.0 milliEquivalents/liter, (n) abnormal baseline Thyroid Stimulating Hormone (TSH) greater than 1.5 times the upper limit of normal, (o) any patient unwilling or expressing uncertainty about being able to refrain from daily alcohol use (even if at moderate levels) or illegal drugs while taking the study medication, including medical marijuana, (p) any recent history of suspected substance abuse or dependence, (q) history of misuse of a stimulant, (r) current suicidal ideation or baseline Patient Health Questionnaire (PHQ-9) score of 20 or greater, (s) history of nephrolithiasis, (t) is pregnant or who is planning to become pregnant during the study period, (u) unable to identify a primary care physician, (v) history of cardiovascular disease (i.e. recent history of myocardial infarction, stroke, shortness of breath, chest pain) that could increase vulnerability to the sympathomimetic effects of a stimulant-like drug.

### **Screening/Enrollment**

Eligibility is assessed via an initial telephone screen to determine whether DSM criteria for BED or BN are met and whether any inclusion/exclusion criteria as detailed are/are not satisfied.

Those who do not meet criteria are provided with a referral list for treatment/care. Those who meet criteria on initial screening are asked to complete baseline assessments, including labs and written informed consent, prior to invitation for an in-person clinical interview. The assessments are completed again after treatment in the first medication group, at baseline 2 prior to crossing

over to the second medication group, and then after completion of the second medication group.

Labs completed at baseline include complete blood count, complete metabolic panel, TSH, and if female, a pregnancy test. At study physician's discretion, additional labs may be ordered during the study as clinically appropriate.

### **Safety/Tolerability**

Inclusion and exclusion criteria during the screening process will help to exclude patients who might suffer side effects from the treatment (e.g., low potassium) while assuring that those entered will have the appropriate diagnosis to possibly benefit from this treatment. At the first study visit, the study physician reviews all inclusion/exclusion criteria as well as all labs again. Any female with confirmed or intended pregnancy is informed and excluded due to potential teratogenicity. Women are counseled specifically that the extra risk of cleft lip and/or palate when taking topiramate during the first trimester is 1 in 500. Physician investigators involved in prescribing Qsymia have taken the REMS training program offered by Vivus (Campbell, CA) in an effort to reduce risk of teratogenicity for women of childbearing potential. The need for consistent use of effective contraception during treatment is encouraged. All participants are given information about Qsymia and the most common side effects at the top doses (e.g., tingling/parasthesias, constipation, dry mouth, abnormal taste, dizziness, insomnia, nausea, depression, blurred vision, low potassium, and angle closure glaucoma [less than 1 in 1000]).<sup>44</sup>

To improve the likelihood of safety during the trial, any patients with baseline potassium levels between 3.0-3.5 milli-equivalents/liter would be encouraged to ingest foods higher in potassium.

To reduce the risk of side effects such as insomnia, patients are instructed to take Qsymia in the

morning, with or without food. To reduce the risk of renal stones, parasthesias, or dry mouth, patients are instructed to drink 8 glasses of water per day. Patients are told to report any symptoms of blurred vision and/or eye pain. In such cases Qsymia is discontinued and patients are referred for intra-ocular pressure measurement within one day of symptom onset.

## Measures

Measures include demographic data, vital signs (including heart rate, blood pressure, weight), Eating Disorder Examination (EDE),<sup>45</sup> Eating Disorder Examination Questionnaire (EDE-Q),<sup>46</sup> Yale-Brown Obsessive Compulsive Scale for Binge Eating (YBOCS-BE),<sup>47</sup> Three Factor Eating Questionnaire (TFEQ),<sup>48</sup> Yale Food Addiction Scale (YFAS),<sup>49</sup> Binge Eating Scale (BES),<sup>50</sup> and Patient Health Questionnaire (PHQ-9).<sup>51</sup> Major assessment points are scheduled prior to randomization (baseline 1), after 12 weeks of treatment (post-treatment 1), prior to the crossover (baseline 2), after the 12 week crossover (post-treatment 2), and after follow-up months 1 (follow-up 1) and 2 (follow-up 2). In addition, vital signs are recorded at each of the 12 medication visits. Weekly online binge trackers are used to record participants' self-reported binge and/or purge episodes.

The primary and secondary study efficacy outcomes are listed in **Table 1**.

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**Table 1.** Primary and secondary study efficacy outcomes

<p><b>Primary study outcome</b>                  Number of binge eating days per week from EDE (average over 28 days)</p> <p><b>Secondary study outcomes</b>                  Number of binge eating episodes from EDE (average per 28 days)                  Abstinence (no binge eating episodes) from EDE over past 28 days                  Binge Eating Scale (BES)                  Patient Health Questionnaire (PHQ-9)                  Eating Disorder Examination Questionnaire (EDE-Q)                      Dietary restraint subscale                      Eating concern subscale                      Weight concern subscale                      Shape concern subscale                      Global Score for all subscales                  Three-Factor Eating Questionnaire (TFEQ)                      Cognitive restraint of eating subscale                      Disinhibition score subscale                      Hunger score subscale                  Yale-Brown Obsessive Compulsive Scale modified for binge eating (YBOCS-BE)                  Yale Food Addiction Scale (YFAS)</p>
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### Data Analysis Plan

The primary outcome measure will be the average number of binge eating days per week, as assessed by the EDE. Secondary outcome measures include the average number of binge eating episodes and percentage abstinence from binge eating. Throughout the study, weekly online binge trackers are used to record participants’ binge and/or purge episodes per week per patient report. Vitals (weight, heart rate, blood pressure) and side effects will be assessed at each visit to ensure safety. See Table 2. In addition, any treatment-emergent adverse events will be recorded.

**Table 2. Assessment Schedule**

Measures	Baseline1 (Wk0)	Med Visit 1 (Wk0)	Med Visit 2 (Wk2)	Med Visit 3 (Wk4)	Med Visit 4 (Wk8)	Med Visit 5 PT1 (Wk12)	Med Visit 6 BL2 (Wk14)	Med Visit 7 (Wk16)	Med Visit 8 (Wk18)	Med Visit 9 (Wk22)	Med Visit 10 PT2 (Wk26)	Follow Up Med Visit 11 (Wk30)	Follow Up Med Visit 12 (Wk34)
Informed Consent	X												
Demographics	X												
Vitals (Weight/HR/BP) & Side Effects	X	X	X	X	X	X	X	X	X	X	X	X	X
EDE	X					X	X				X		
BES	X					X	X				X		
PHQ-9	X					X	X				X		
EDE-Q	X					X	X				X		

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TFEQ	X					X	X				X		
YBOCS-BE	X					X	X				X		
YFAS	X					X	X				X		

\*Abbreviation Key: Eating Disorder Examination (EDE), Binge Eating Scale (BES), Patient Health Questionnaire (PHQ-9), Eating Disorder Examination Questionnaire (EDE-Q), Three Factor Eating Questionnaire (TFEQ), Yale-Brown Obsessive Compulsive Scale for Binge Eating (YBOCS-BE), and Yale Food Addiction (YFAS), Baseline Assessment (BL1, BL2), Post-Treatment Assessment (PT1, PT2). Crossover occurs at Medication Visit 6 with two-week washout prior.

Primary and secondary study outcomes will be compared using intention-to-treat (ITT) analysis for all randomized patients. Mixed-effects models with fixed effects for treatment, follow-up period, treatment by period (interaction representing carry-over effect), and eating disorder diagnosis (used to stratify randomization) will be used to estimate the treatment effect. Mixed-effects models include subject-level random effects to account for repeated measurements within subjects. Non-significant treatment by period interaction ( $p \geq 0.05$ ) will be removed from the model before estimating the final treatment effect. In the case of a significant treatment by period interaction ( $p < 0.05$ ) the analysis will revert to that of a standard parallel arm randomized trial using data from the first period only. A p-value of less than 0.05 is considered statistically significant and the Kenward-Roger degrees of freedom approximation will be used in tests of significance from mixed models.

Where appropriate normal mixed-effects models will be used to analyze continuous study outcomes, otherwise data will be transformed (e.g.  $\log[\text{value} + 1]$ ) or alternatively analyzed using methods appropriate for non-normal continuous data (e.g. log-normal). Outcomes that are binary, categorical or count data will be analyzed using appropriate mixed-effects models (e.g. logistic, multinomial or Poisson). While patients are stratified by eating disorder and it is anticipated subject characteristics by treatment sequence allocation will be balanced within

strata, we will conduct secondary analyses adjusting for important baseline covariates (e.g. gender), sample size permitting. Secondary analyses will also include using compliance as a covariate in addition to the total drug received as an exposure. Finally, additional analysis will assess the sensitivity of findings to the missing at random assumption associated with using mixed models according to assumed worst and best-case scenarios.

## **Discussion**

While current treatments for BED and BN are helpful for many, a substantial proportion of patients with BN or BED do not experience symptomatic improvement with current psychotherapy or pharmacotherapy treatments. Therefore, new treatment options are needed. One such option involves repurposing Qsymia (phentermine/topiramate ER), which has been FDA-approved for the treatment of obesity. Topiramate, one of the components of Qsymia, has shown efficacy in reducing disordered eating in both BED and BN. However, its utility has been limited by side effects, which have led to high dropout rates, especially at higher doses.

The described protocol highlights the background and rationale for the first randomized clinical trial to test the use of Qsymia (phentermine/topiramate ER) to treat BED and BN.

Phentermine/topiramate ER is an example of a dual combination agent which, due to opposing side effect profiles and pharmacokinetics, may potentially improve efficacy and/or reduce side effects. This may result in lowered doses and less discontinuation for BED and BN compared to monotherapy.

Given that this is the first RCT to use phentermine/topiramate ER in this population (patients

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with active BN), the protocol was designed to pose the least possible risk to participants. The study's inclusion/exclusion criteria are strict, with no patients with a history of anorexia nervosa or a BMI < 21 included, for instance. Also, during the trial, patients must attend multiple study visits to track weight and vital signs in recognition of this proof-of-concept study. Another important feature is that the dosing of the study medication is not fixed. The study physician may dose the medication or placebo based on side effects as well as efficacy. For example, if a study participant finds a lower dose of study drug effective in reducing symptoms yet begins to report side effects, no further increase in dosage will occur unless symptoms recur. If the study participant reports intolerable side effects, the dose will be lowered.

The protocol's use of a crossover design was chosen to allow participants to serve as their own controls, thus increasing power without the need to recruit additional subjects (hence reducing costs). However, limitations include the risk of carry-over or learned effects, which can confound the estimates of treatment effects. The data analysis will assess for the presence or degree of these carry-over effects.

Most RCTs investigating medications for BED and BN are short-term and do not allow evaluation of the length of symptom remission after medications (or placebo) are stopped. Hence, an additional feature of the protocol's design is its inclusion of an 8-week follow-up period to examine binge eating symptoms after the cessation of all study medications (Qsymia or placebo).

In summary, the described protocol has many features which enhance its potential impact as a first step towards investigating phentermine-topiramate ER's efficacy and safety. These include

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(1) a background section that thoroughly explains why new treatment options for BED and BN are needed; (2) the existence of a compelling rationale for why phentermine-topiramate ER, an FDA-approved medication for obesity, should be repurposed for BED and BN, (3) and the choice of a distinctive design, a crossover RCT with an 8-week follow-up to examine length of symptom remission.

### **Trial Status**

Recruitment for this trial has been ongoing since August/September 2015.

### **Acknowledgement**

The authors gratefully acknowledge the research assistance of Hannah Toyama and Sarah Pajarito. We also acknowledge Vivus Pharmaceuticals for supplying Qsymia (phentermine/topiramate ER) and identical appearing placebo.

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